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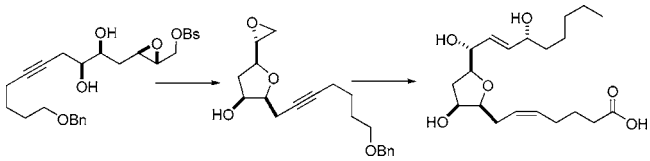
Synthesis of the Enediol Isofurans, Endogenous Oxidation Products of Arachidonic Acid

Douglass F. Taber* and Zhe Zhang

Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716

taberdf@udel.edu

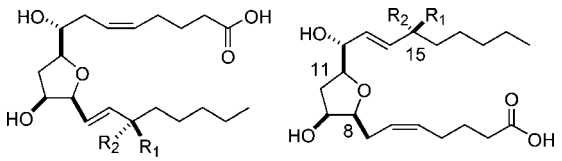
Received September 8, 2005



Isofurans (IsoF's) are a new class of human arachidonic acid oxidation products. They are produced in vivo by a free radical mechanism, independent of the cyclooxygenase enzymes. These new compounds are available from natural sources only in microgram quantities as mixtures. The enantioselective preparation of two enediol isofurans, 15-*epi*-ent-SC-Δ^{13}-8-IsoF and ent-SC-Δ^{13}-8-IsoF, is described. A key transformation in the synthesis is the selective cascade cyclization of a diol epoxide benzenesulfonate to give the substituted tetrahydrofuran skeleton of the isofurans. This synthesis will make these metabolites available for physiological evaluation.

Introduction

Isofurans (IsoF's) are a new class of human arachidonic acid oxidation products.[1,2] They are produced in vivo by a free radical mechanism, independent of the cyclooxygenase enzymes. Because these compounds are tetrahydrofuran derivatives that are related biosynthetically to the isoprostanes, they were termed isofurans.[3] When oxygen tension is increased in vitro or in vivo isofuran formation increases more rapidly than does isoprostane formation.



1a R_1 = OH, R_2 = H
1b R_1 = H, R_2 = OH

2a R_1 = OH, R_2 = H
2b R_1 = H, R_2 = OH

Even though they are nonenzymatic oxidation products, the isoprostanes have been found to have significant physiological activity.[4] It is therefore important to also investigate the physiological role of the IsoF's. We have previously reported[5] a stereodivergent synthesis of the SC-Δ^{13}-9-IsoFs (**1a** and **1b**). We now report a general route to the other class of isofurans, the enediol isofurans, represented by 15-*epi*-ent-SC-Δ^{13}-8-IsoF (**2a**) and ent-SC-Δ^{13}-8-IsoF (**2b**).

Results and Discussion

Synthetic Approach. Our interest was to develop a flexible route for the construction of the enediol isofurans. We sought an advanced intermediate from which each of the enantiomerically pure diastereomers could be prepared. One such advanced intermediate would be the substituted tetrahydrofuran **3** (Scheme 1).

We envisioned that **3** could be prepared by cascade cyclization[6] of the diol epoxide **4**. Although there are four different modes of epoxide opening available to the diol **4**, it seemed likely that exo cyclization would dominate over endo cyclization and that five-membered-ring formation would be faster than

(1) Fessell, J. P.; Porter, N. A.; Moore, K. P.; Sheller, J. R.; Roberts, L. J., II *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 16713.

(2) An IsoF-type compound has been reported as a product from enzymatic oxidation of arachidonic acid: (a) Pace-Asciak, C. *Biochemistry* **1971**, *10*, 3664. (b) Bild, G. S.; Bhat, S. G.; Ramadoss, C. S.; Axelrod, B.; Sweeley, C. C. *Biochem. Biophys. Res. Commun.* **1978**, *81*, 486. Neither the relative nor the absolute configuration of this product was assigned.

(3) For isofuran nomenclature, see: Taber, D. F.; Morrow, J. D.; Roberts, L. J. *Prostaglandins Other Lipid Mediators* **2004**, *73*, 47.

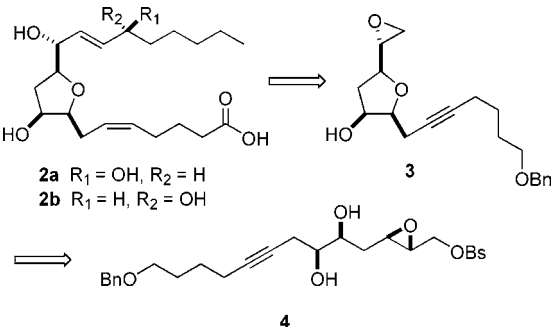
(4) For leading references to the physiological activity of the isoprostanes, see: Fessel, J. P.; Hulette C.; Powell S.; Roberts, L. J., II; Zhang, J. *J. Neurochem.* **2003**, *85*, 645. Nothing is yet known about the physiological activity of the isofurans.

(5) Taber, D. F.; Pan, Y.; Zhao, X. *J. Org. Chem.* **2004**, *69*, 7234.

(6) (a) Taber, D. F.; Bhamidipati, R. S.; Thomas, M. L. *J. Org. Chem.* **1994**, *59*, 3442. (b) Sivakumar, M.; Borhan, B. *Tetrahedron Lett.* **2003**, *44*, 5547.

10.1021/jo051889a CCC: $33.50
Published on Web 12/31/2005

SCHEME 1



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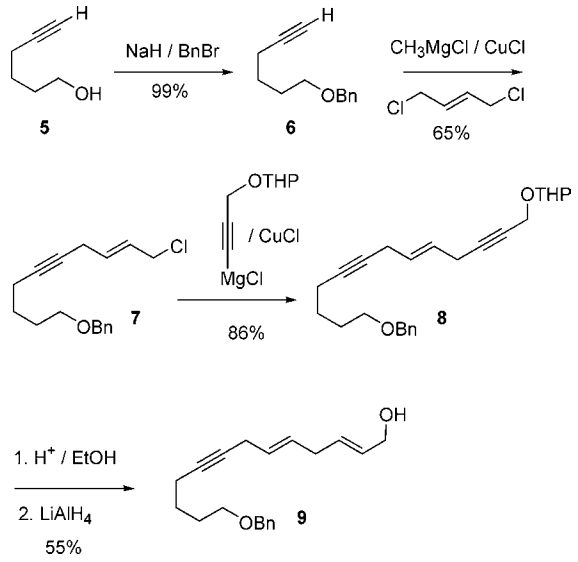
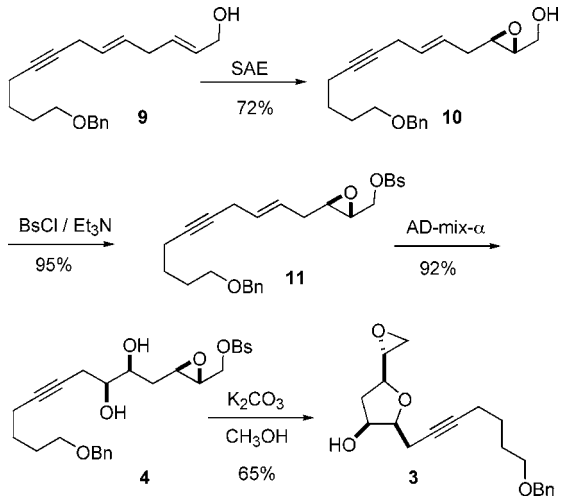


four-membered-ring formation. Ring closure of the intermediate alkoxide would then lead to the epoxide **3**. As the diol epoxide **4** would be prepared by the Sharpless asymmetric epoxidation and dihydroxylation reactions, the relative and absolute configuration of **3** could be easily varied by using the opposite enantiomers of the catalysts. We therefore expect that the synthetic approach outlined here will allow the preparation of any of the enantiomerically pure diastereomers of the different regioisomers of the enediol isofurans.

Preparation of the Diene Alcohol 9. We projected that the diol epoxide **4** could be prepared (Scheme 2) from the diene **9**, which would be available by deprotection and reduction of the diyne **8**. We envisioned a linchpin construction[7] of **8**, by sequential Cu-mediated coupling of the commercially available *trans*-1,4-dichloro-2-butene with **6**, then with THP-protected propargyl alcohol.

Starting with 5-hexyne-1-ol **5**, the free alcohol was protected first with benzyl bromide. The resulting benzyl ether **6** was treated with CH_3MgCl to form the corresponding Grignard reagent and then reacted with *trans*-1,4-dichloro-2-butene to yield the mono-alkylation product **7**.[7,8] Only a trace amount (less than 1%) of the doubly alkylated product was observed. After optimization, the ratio between S_N2 and S_N2' product (not pictured) was about 10:1, and the S_N2' byproduct could be easily removed by flash chromatography. Coupling of the chloride **7** with the THP protected propargyl alcohol led to the diyne **8**. Deprotection[9] followed by the reduction of the diyne **8** with use of LAH in THF[10] at reflux yields the diene **9**.

SCHEME 3



Preparation of the Diol Epoxide 4 and Its Cyclization. The diene **9** (Scheme 3) was carried on to the epoxy alcohol **10** by the Sharpless asymmetric epoxidation.[11] The derived benzenesulfonate **11** was subjected to the Sharpless asymmetric dihydroxylation[12] with use of AD-mix-α to afford the desired diol epoxide **4**.

With **4** in hand, we were ready to attempt the key cyclization.[6] We tried the reaction with both potassium *tert*-butoxide in THF[13] and potassium carbonate in methanol.[14] The reaction in methanol was cleaner, but the timing was critical. The reaction was complete after 4 h at room temperature. A shorter time gave incomplete conversion, while longer time gave partial decomposition of the product.

Neither the Sharpless asymmetric epoxidation nor the dihydroxylation proceeds with perfect enantiocontrol. We therefore expected that **4** would be contaminated with minor amounts of other diastereomers. We were pleased to observe that the epoxide **3** was easily purified by flash chromatography.

Construction of the Upper Side Chain. To complete the preparation (Scheme 4) of the upper side chain, it was necessary to convert the epoxide **3** to the protected aldehyde **14**. Since the epoxide of **3** was already primed for S_N2 opening, simple treatment with the sulfonium ylide[15] afforded the diol **12**. Protection followed by gentle oxidative cleavage[16] led to the sensitive aldehyde **14**. Horner−Emmons[17] condensation then gave the enone **15**.

(7) For the development of this linchpin approach to the assembly of oxidized fatty acid metabolites, see: Taber, D. F.; Zhang, Z. *J. Org. Chem.* **2005**, *70*, 8093.

(8) (a) Gaudin, J. M.; Morel, C. *Tetrahedron Lett.* **1990**, *31*, 5749. (b) Gaoni, Y.; Leznoff. C. C.; Sondheimer, F. *J. Am. Chem. Soc.* **1968**, *90*, 4940.

(9) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

(10) Grant, B.; Djerassi, C. *J. Org. Chem.* **1974**, *39*, 968.

(11) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.

(12) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

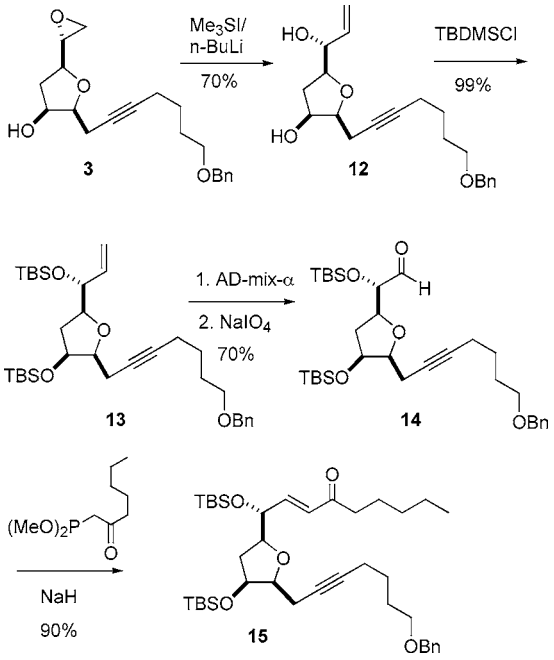
(13) Ho, D. K.; McKenzie, A. T.; Byrn, S. R.; Cassady, J. M. *J. Org. Chem.* **1987**, *52*, 342.

(14) Burke, S. D.; Jiang, L. *Org. Lett.* **2001**, *2*, 1953.

(15) (a) Alcaraz, L.; Harnett, J. J.; Mioskowski, C.; Martel, J. P.; Gall, T. L.; Shin, D. S.; Falck, J. R. *Tetrahedron Lett.* **1994**, *35*, 5449. (b) Bode, J. W.; Carreira, E. M. *J. Org. Chem.* **2001**, *66*, 6410.

(16) Daumas, M.; Vo-Quang, Y.; Vo-Quang, L.; Goffic, F. L. *Synthesis* **1989**, 64.

SCHEME 4



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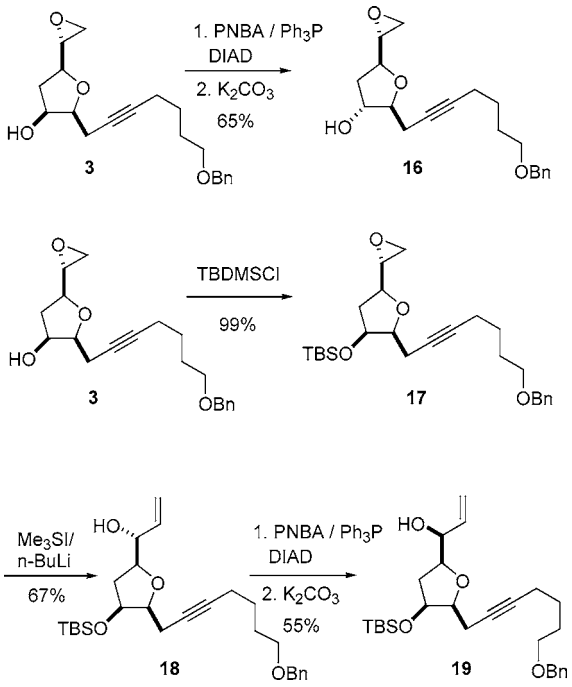
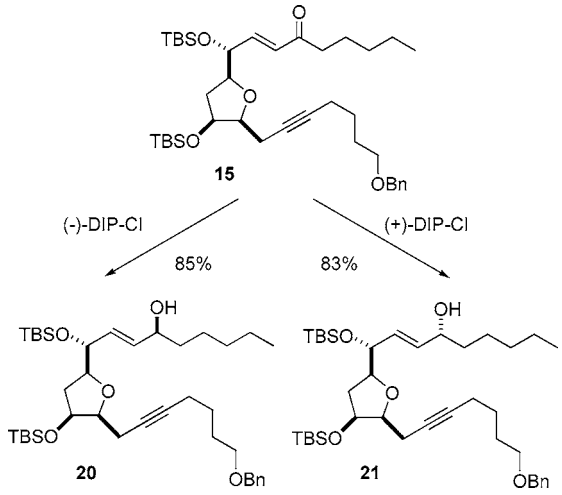


Inversion of the Second Alcohols. To ensure stereodivergence, it was necessary (Scheme 5) to invert the alcohols at C-9 and C-12. The inversion to prepare **16** was a particularly delicate transformation, as **3** was prone to further cyclization by intramolecular addition of the secondary alcohol to the epoxide. Nevertheless, the secondary alcohols at both C-9 and C-12 participated efficiently in Mitsunobu inversion[18] to give, after methanolysis, the inverted alcohols **16** and **19**.

(17) (a) Horner, L.; Hoffmann, H. M. R.; Wippel, H. G. *Chem. Ber.* **1958**, *91*, 61. (b) Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.

(18) (a) Mitsunobu, O. *Synthesis* 1981, 1. (b) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.

SCHEME 6



Diastereoselective Reduction of Enone 15. Continuing with the synthesis (Scheme 6), the next step was the reduction of the enone **15**. We were pleased to observe that the mixture of diastereomeric alcohols **20** and **21** from $NaBH_4$ and $CeCl_3 \cdot 7H_2O$ reduction[19] was easily separable by TLC. Excellent diastereocontrol in favor of **20** or **21** could be achieved by using the appropriate enantiomer of DIP-Cl in the reduction.[20]

Construction of the Lower Chain and Synthesis of the Isofurans. With each of the alcohols **20** and **21** in hand, the next step (Scheme 7) was silyl protection, followed by partial hydrogenation with P-2 Ni catalyst[21] to afford the dienes **24** and **25**. We found that the P-2 Ni catalyst did not require protection from air. The resulting catalyst is efficient for the partial hydrogenation for the alkynes. Even after stirring under an H_2 atmosphere for 24 h, we did not observe even trace amounts of over-hydrogenation products. Debenzylation of diene **24** and **25** with lithium and naphthalene[22] affords the desired alcohols **26** and **27**, respectively.

The final steps in the synthesis (Scheme 8) were the oxidation of the primary alcohol of **26** and **27** to the corresponding acids, and deprotection to yield the final isofurans. While PDC in wet DMF served to convert the alcohol **26** to the acid **29**, this protocol worked poorly with the alcohol **27**. Happily, a two-step protocol of Dess−Martin oxidation followed by the $NaClO_2$ oxidation[24] delivered the desired acid **29** in good yield. Desilylation with TBAF then afforded the desired *epi*-ent-SC-Δ^{13}-8-IsoF (**2a**) and ent-SC-Δ^{13}-8- IsoF (**2b**).

Conclusion

We have established what we expect will be a general route to the enediol isofurans. The key steps include the cascade cyclization of the diol **4** to the epoxide **3** and the diastereoselective DIP-Cl reduction of enone **15**. This approach will make

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(20) (a) Beardley, D. A.; Fisher, G. B.; Goralski, C. T.; Nicholson, W. L.; Singaram, B. *Tetrahedron Lett.* **1994**, *35*, 1151. (b) Ramachandran, P. V.; Gong, B.; Brown, H. C. *Tetrahedron Lett.* **1994**, *35*, 2141.

(21) (a) Brown, C. A.; Ahuja, V. K. *J. Org. Chem.* **1973**, *38*, 2226. (b) Taber, D. F.; Hoerrner, R. S. *J. Org. Chem.* **1992**, *57*, 441. (c) Magatti, C. V.; Kaminski, J. J.; Rothberg, I. *J. Org. Chem.* **1991**, *56*, 3102.

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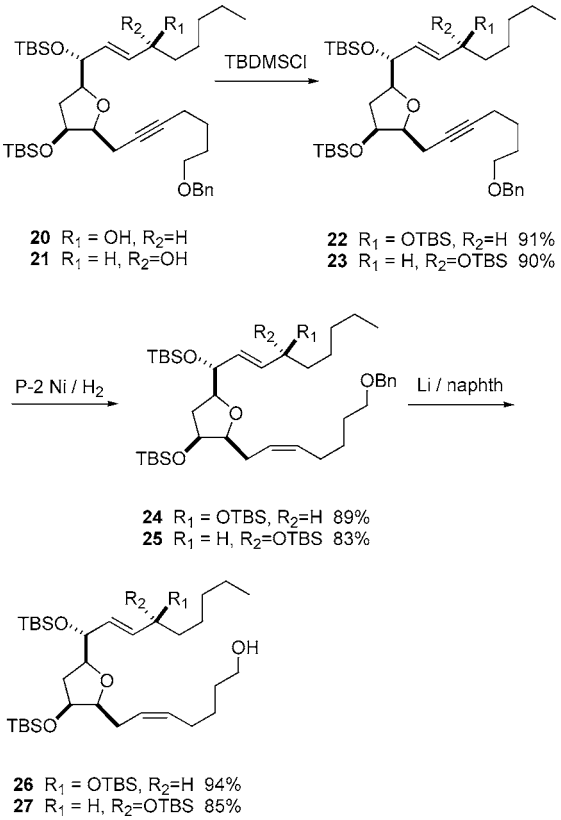
(23) (a) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1978**, *5*, 399. (b) Williams, D. R.; Meyer, K. G. *J. Am. Chem. Soc.* **2001**, *123*, 765.

(24) Nicolaou, K. C.; Sasmal, P. K.; Xu, H.; Namoto, K.; Ritzen, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4225.

SCHEME 7



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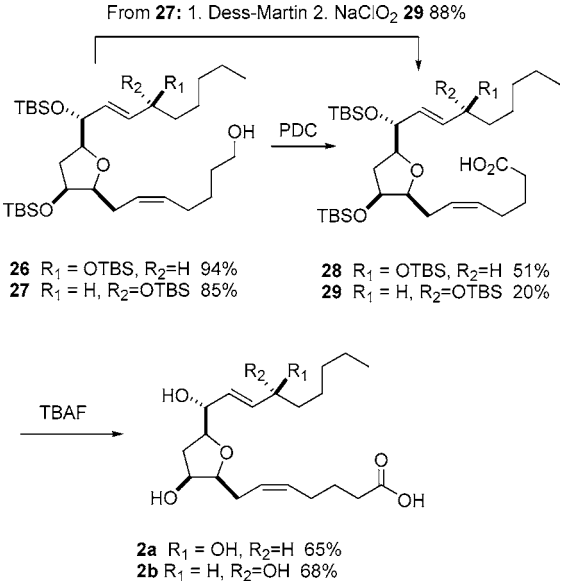

each of the enediol isofurans, previously known only in microgram quantities as mixtures, available in sufficient quantity to assess their individual physiological activity.

Experimental Section

Chlorobenzyl Ether 7. To a solution of benzyl ether **6**[25] (5.0 g, 26.6 mmol) in THF (20 mL) was added a solution of CH_3MgCl (2.0 M solution in THF, 17.3 mL, 34.6 mmol) at 50 to 60 °C under N_2. After addition, the reaction mixture was stirred at 50 to 60 °C for 2 h and then cannula transferred to a solution of *trans*-1,4-dichloro-2-butene (6.65 g, 53.3 mmol) and CuCl (264 mg, 2.66 mmol) in THF (20 mL) at 50 to 60 °C under N_2. The resulting mixture was heated to reflux for 4 h. After being cooled to room temperature, the reaction mixture was partitioned between saturated aqueous NH_4Cl and ether. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give chlorobenzyl ether **7** as a colorless oil (4.78 g, 17.3 mmol, 65% yield): TLC R_f(MTBE/petroleum ether = 1:30) = 0.45; ^{1}H NMR δ 1.59−1.72 (m, 4H), 2.19−2.22 (m, 2H), 2.94 (br s, 2H), 3.49 (t, J = 5.4 Hz, 2H), 4.05 (d, J = 7.5 Hz, 2H), 4.49 (s, 2H), 5.77−5.88 (m, 2H), 7.33 (br s, 5H); ^{13}C NMR δ u 138.5, 82.7, 76.2, 72.8, 69.8, 44.6, 28.9, 25.6, 21.6, 18.5, d 130.2, 128.3, 127.6, 127.5, 127.1; IR (cm^{-1}) 2940, 1717, 1453; MS *m*/*z* (%) 275 (15), 167 (100), 149 (45); HRMS calcd for $C_{17}H_{20}OCl$ (M) 275.1204, obsd 275.1203.

Diyne 8. To a solution of tetrahydro-2-(2-propynyloxyl)-2*H*-pyran (7.3 g, 52.1 mmol) in THF (30 mL) was added a solution of CH_3MgCl (2.0 M solution in THF, 14.3 mL, 28.6 mmol) at 50 to 60 °C under N_2. After addition, the reaction mixture was stirred at 50 to 60 °C for 3 h and then cannula transferred to a solution of chlorobenzyl ether **7** (7.2 g, 26.0 mmol) and CuCl (258 mg, 2.6 mmol) in THF (30 mL) at 50 to 60 °C under N_2. The resulting mixture was heated to reflux for 3 h. After being cooled to room temperature, the reaction mixture was partitioned between saturated aqueous NH_4Cl and ether. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give diyne **8** as a colorless oil (8.50 g, 22.4 mmol, 86% yield): TLC R_f(MTBE/petroleum ether = 1:10) = 0.35; ^{1}H NMR δ 1.56−1.72 (m, 10H), 2.17−2.22 (m, 2H), 2.89 (br s, 2H), 2.97 (br s, 2H), 3.47 (t, J = 6.4 Hz, 2H), 3.50−3.53 (m, 1H), 3.79−3.85 (m, 1H), 4.20 (dt, J = 17.4, 2.1 Hz, 1H), 4.30 (dt, J = 17.4, 2.1 Hz, 1H), 4.48 (s, 2H), 4.79 (t, J = 3.4 Hz, 1H), 5.65 (br s, 2H), 7.30 (br s, 5H); ^{13}C NMR δ u 138.6, 83.5, 82.1, 77.7, 77.1, 72.8, 69.9, 62.0, 54.6, 30.2, 28.9, 25.7, 25.3, 21.8, 21.7, 19.1, 18.6, d 128.3, 127.6, 127.5, 126.8, 125.2, 96.7; IR (cm^{-1}) 2942, 1453, 1023; MS *m*/*z* (%) 380 (10), 167 (55); HRMS calcd for $C_{25}H_{32}O_3Na$ (M + Na) 403.2249, obsd 403.2248.

Diene 9. To a solution of diyne **8** (9.0 g, 23.7 mmol) in EtOH (180 mL) was added PPTS (595 mg, 2.37 mmol) at room temperature. After addition, the reaction mixture was stirred at 55 °C for 6 h, then concentrated. The residue was chromatographed to give the free alcohol as a colorless oil (6.45 g, 21.8 mmol, 92% yield): TLC R_f(MTBE/petroleum ether = 1:4) = 0.25; ^{1}H NMR δ 1.55−1.73 (m, 4H), 2.18−2.21 (m, 2H), 2.89 (br s, 2H), 2.94−2.96 (m, 2H), 3.47 (t, J = 6.4 Hz, 2H), 4.24 (br s, 2H), 4.49 (s, 2H), 5.66−5.67 (m, 2H), 7.33 (br s, 5H); ^{13}C NMR δ u 138.5, 82.5, 82.2, 80.2, 77.1, 72.9, 69.9, 51.3, 28.9, 25.6, 21.7, 21.6, 18.6, d 128.4, 127.6, 127.5, 126.9, 125.2; IR (cm^{-1}) 3300, 2862, 1104; MS *m*/*z* (%) 319 (M + Na, 100), 199 (12), 128 (20); HRMS calcd for $C_{20}H_{24}O_2Na$ (M + Na) 319.1674, obsd 319.1669.

To a suspension of $LiAlH_4$ (2.59 g, 68.1 mmol) in THF (220 mL) was added a solution of the alcohol (10.1 g, 34.1 mmol) in THF (20 mL) at 0 °C under N_2. After addition, the reaction mixture was heated to reflux for 24 h. The reaction mixture was cooled in an ice bath, and cold water (2.6 mL) was added dropwise over 5 min. After 30 min of vigorous stirring, aq NaOH (15% w/v, 2.6 mL) was added, and the mixture was stirred for an additional 30 min. Then water (7.8 mL) was added, and the mixture was stirred for another 30 min. The solid was filtered and then rinsed with diethyl ether. The combined filtrate was concentrated, and the resulting residue was chromatographed to give diene **9** as a colorless oil (6.10 g, 20.5 mmol, 60% yield): TLC R_f(MTBE/petroleum ether = 1:2) = 0.25; ^{1}H NMR δ 1.55−1.72 (m, 5H), 2.18−2.20 (m, 2H), 2.75 (br s, 2H), 2.86−2.88 (m, 2H), 3.47 (t, J = 6.4 Hz, 2H), 4.06 (br s, 2H), 4.48 (s, 2H), 5.45−5.68 (m, 4H), 7.33 (br s, 5H); ^{13}C NMR δ u 138.5, 81.9, 77.5, 72.8, 69.9, 63.6, 34.8, 28.9, 25.7, 21.9, 18.6, d 130.8, 129.9, 129.0, 128.3, 127.6, 127.5, 126.1; IR

(25) Takami, K.; Mikami, S.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2003**, *68*, 6627.

(cm^{-1}) 3300, 2861, 1101; MS *m*/*z* (%) 281 (M − H, 100), 263 (10); HRMS calcd for $C_{20}H_{26}O_2Na$ (M + Na) 321.1831, obsd 321.1824.

Epoxide 10. To a solution of (−)-diethyl D-tartrate (2.28 g, 11.07 mmol) in dry CH_2Cl_2 (50 mL) was added titanium(IV) isopropoxide (3.09 g, 10.88 mmol) at −30 to −20 °C. The mixture was stirred for 30 min. A solution of diene **9** (3.0 g, 10.07 mmol) in CH_2Cl_2 (65 mL) was added, and the mixture was sirred at −30 to −20 °C for 20 min. *tert*-Butyl hydroperoxide (4.75 mL, 5.6 M in CH_2Cl_2, 26.57 mmol) was then added dropwise over 10 min. The resulting mixture was stirred at −30 to −20 °C for 15 h. Aqueous (+)-L-tartaric acid (10% w/w, 21.6 mL) was added, then the mixture was stirred at −20 °C for 30 min, allowed to warm to room temperature, and stirred for 1 h. Aqueous NaOH (1 N, 59.0 mL) was added at 0 °C, and the resulting mixture was stirred for 1 h. The reaction mixture was then partitioned between water and CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give epoxide **10** as a colorless oil (2.25 g, 7.17 mmol, 72% yield). TLC R_f(MTBE/petroleum ether = 2:1) = 0.45; ^{1}H NMR δ 1.55−1.73 (m, 4H), 1.82−1.85 (m, 1H), 2.17−2.21 (m, 2H), 2.29−2.34 (m, 2H), 2.86−2.89 (m, 2H), 2.91−2.93 (m, 1H), 2.98−3.01 (m, 1H), 3.47 (t, J = 6.4 Hz, 2H), 3.60 (ddd, J = 4.3, 7.1, 12.5 Hz, 1H), 3.86 (ddd, J = 2.6, 5.4, 12.5 Hz, 1H), 4.48 (s, 2H), 5.51−5.55 (m, 1H), 5.63−5.67 (m, 1H), 7.33 (br s, 5H); ^{13}C NMR δ u 138.5, 82.1, 77.2, 72.9, 69.9, 61.5, 34.1, 28.9, 25.6, 22.0, 18.6, d 128.3, 128.2, 127.6, 127.5, 125.4, 57.9, 55.0; IR (cm^{-1}) 3439, 2932, 1098; MS *m*/*z* (%) 315 (M + H, 100), 297(37), 279(15); $[\alpha]_D$ +11 (*c* 2.71, CH_2Cl_2).

Benzenesulfonate 11. To a solution of epoxide **10** (2.25 g, 7.17 mmol) in CH_2Cl_2 (40 mL) was added DMAP (44 mg, 0.36 mmol). The solution was cooled to 0 °C, and Et_3N (2.54 g, 25.10 mmol) was added, followed by benzenesulfonyl chloride (3.17 g, 17.93 mmol) dropwise over 15 min. The mixture was allowed to warm to room temperature and stirred for 3 h. The reaction mixture was then partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give benzenesulfonate **11** as a colorless oil (3.09 g, 6.81 mmol, 95% yield). TLC R_f(MTBE/petroleum ether = 1:1) = 0.55; ^{1}H NMR δ 1.57−1.72 (m, 4H), 2.17−2.21 (m, 2H), 2.24−2.32 (m, 2H), 2.83−2.87 (m, 3H), 2.96−2.98 (m, 1H), 3.47 (t, J = 6.3 Hz, 2H), 3.96 (dd, J = 6.0, 11.4 Hz, 1H), 4.22 (dd, J = 3.6, 11.4 Hz, 1H), 4.48 (s, 2H), 5.46−5.52 (m, 1H), 5.56−5.61 (m, 1H), 7.31 (br s, 5H), 7.55 (t, J = 6.6 Hz, 2H), 7.64 (d, J = 6.6 Hz, 1H), 7.90 (d, J = 6.6 Hz, 2H); ^{13}C NMR δ u 138.6, 135.7, 82.3, 72.9, 70.1, 69.9, 33.8, 28.9, 25.7, 22.0, 18.6, d 134.0, 129.3, 128.7, 128.3, 127.9, 127.6, 127.5, 124.8, 55.7, 54.0; IR (cm^{-1}) 2932, 1448, 1100; MS *m*/*z* (%) 477 (M + Na, 100), 387 (15), 319 (15); HRMS calcd for $C_{26}H_{30}O_5SNa$ (M + Na) 477.1712, obsd 477.1715; $[\alpha]_D$ +26 (*c* 1.61, CH_2Cl_2).

Diol 4. A suspension of AD-mix-α (12.0 g) in *t*-BuOH−H_2O (1:1, v/v, 60 mL) was stirred at room temperature until both phases were clear, then cooled to 0 °C. Methanesulfonamide (572 mg, 6.01 mmol) was added, followed by benzenesulfonate **11** (2.73 g, 6.01 mmol) dropwise over 5 min. The resulting mixture was stirred at 0 °C for 40 h. Solid $NaHSO_3$ (12.4 g) was carefully added to the reaction mixture, which was stirred at room temperature for 1 h. The reaction mixture was then partitioned between EtOAc and brine. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give diol **4** as a colorless oil (2.71 g, 5.55 mmol, 92% yield). TLC R_f(MTBE/petroleum ether = 3:1) = 0.15; ^{1}H NMR (D-MeOH) δ 1.80−1.86 (m, 4H), 1.95−2.01 (m, 3H), 2.06−2.12 (m, 1H), 2.45 (dd, J = 2.3, 4.5 Hz, 2H), 2.59 (dd, J = 6.1, 16.5 Hz, 1H), 2.73 (dd, J = 6.1, 16.5 Hz, 1H), 3.27−3.32 (m, 2H), 3.79 (t, J = 6.4 Hz, 2H), 3.83 (m, 1H), 4.07 (m, 1H), 4.18 (dd, J = 6.5, 11.5 Hz, 1H), 4.62 (dd, J = 2.9, 11.5 Hz, 1H), 4.77 (s, 2H), 7.61 (br s, 5H), 7.92 (t, J = 7.5 Hz, 2H), 8.01 (t, J = 7.5 Hz, 1H), 8.20 (d, J = 7.5 Hz, 2H); ^{13}C NMR δ u 139.8, 137.2, 82.4, 77.8, 73.8, 72.2, 70.9, 36.2, 29.8, 26.8, 24.3, 19.2, d 135.3, 130.6, 129.4, 129.0, 128.9, 128.6, 73.6, 71.1 55.7, 55.1; IR (cm^{-1}) 3348, 3266, 2932; MS *m*/*z* (%) 511 (M + Na, 100), 413 (10), 239 (15); HRMS calcd for $C_{26}H_{32}O_7SNa$ (M + Na) 511.1766, obsd 511.1771; $[\alpha]_D$ +17 (*c* 2.81, CH_2Cl_2).

Epoxide 3. To a solution of diol **4** (2.66 g, 5.45 mmol) in MeOH (110 mL) was added finely powdered K_2CO_3 (1.50 g, 10.9 mmol). The mixture was stirred at room temperature for 4 h. Then the mixture was concentrated and the residue was partitioned between CH_2Cl_2 and water. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give epoxide **3** as a colorless oil (1.18 g, 3.54 mmol, 65% yield). TLC R_f(MTBE/petroleum ether = 3:1) = 0.55; ^{1}H NMR δ 1.56−1.71 (m, 5H), 2.17−2.22 (m, 3H), 2.54 (dt, J = 2.4, 7.1 Hz, 2H), 2.62 (dd, J = 3.0, 4.4 Hz, 1H), 2.83 (t, J = 4.4 Hz, 1H), 3.22−3.24 (m, 1H), 3.46 (t, J = 6.3 Hz, 2H), 3.84 (dt, J = 3.1, 10.2 Hz, 1H), 4.17−4.22 (m, 2H), 4.48 (s, 2H), 7.33 (br s, 5H); ^{13}C NMR δ u 138.5, 81.6, 76.4, 72.8, 69.8, 45.6, 34.8, 28.9, 25.6, 19.5, 18.6, d 128.3, 127.6, 127.5, 82.7, 77.6, 71.6, 53.5; IR (cm^{-1}) 3449, 2938, 2861; MS *m*/*z* (%) 353 (M + Na, 100), 331 (15), 277 (15); HRMS calcd for $C_{20}H_{26}O_4Na$ (M + Na) 353.1729, obsd 353.1731; $[\alpha]_D$ +30 (*c* 1.52, CH_2Cl_2).

Alkene 12. To a suspension of Me_3SI (1.97 g, 9.67 mmol) in THF (58 mL) was added *n*-BuLi (2 M solution in hexane, 4.3 mL) at −20 to −10 °C under N_2. Then the mixture was stirred at −20 to −10 °C for 1 h. A solution of epoxide **3** (638 mg, 1.93 mmol) in THF (2 mL) was added dropwise. The resulting mixture was allowed to warm to room temperature slowly and stirred for 10 h. The reaction mixture was then partitioned between CH_2Cl_2 and saturated aqueous NH_4Cl. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give alkene **12** as a colorless oil (465 mg, 1.35 mmol, 70% yield). TLC R_f(MTBE/petroleum ether = 2:1) = 0.65; ^{1}H NMR δ 1.52−1.59 (m, 2H), 1.65−1.72 (m, 2H), 1.92 (dd, J = 3.3, 14.3 Hz, 1H), 2.11 (dd, J = 3.3, 10.0 Hz, 1H), 2.14−2.20 (m, 2H), 2.52−2.55 (m, 2H), 3.01 (br s, 1H), 3.46 (t, J = 6.3 Hz, 2H), 3.59 (br d, J = 9.1 Hz, 1H), 3.78 (dt, J = 2.7, 9.5 Hz, 1H), 4.09−4.13 (m, 2H), 4.40−4.42 (m, 1H), 4.47 (s, 2H), 5.20 (dt, J = 1.6, 10.6 Hz, 1H), 5.36 (dt, J = 1.7, 17.2 Hz, 1H), 5.73 (ddd, J = 5.0, 10.6, 17.2 Hz, 1H), 7.32 (br s, 5H); ^{13}C NMR δ u 138.5, 116.4, 81.4, 76.7, 72.9, 69.9, 33.5, 28.9, 25.6, 19.4, 18.6, d 136.3, 128.3, 127.6, 127.5, 82.5, 80.3, 72.7, 71.1; IR (cm^{-1}) 3339, 2860, 1453; MS *m*/*z* (%) 367 (M + Na, 100); HRMS calcd for $C_{21}H_{28}O_4Na$ (M + Na) 367.1885, obsd 367.1894; $[\alpha]_D$ +38 (*c* 0.79, CH_2Cl_2).

Silyl Ether 13. To a solution of alkene **12** (162 mg, 0.47 mmol) in CH_2Cl_2 (7.5 mL) was added imidazole (177 mg, 2.59 mmol) and TBDMSCl (355 mg, 2.36 mmol) at 0 °C. The resulting mixture was allowed to warm to room temperature slowly and stirred for 12 h. The reaction mixture was then partitioned between CH_2Cl_2 and water. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give silyl ether **13** as a colorless oil (268 mg, 0.47 mmol, 99% yield). TLC R_f(MTBE/petroleum ether = 1:10) = 0.55; ^{1}H NMR δ 0.02 (s, 3H), 0.05 (s, 3H), 0.06 (br s, 6H), 0.88 (s, 9H), 0.89 (s, 9H), 1.53−1.58 (m, 2H), 1.65−1.70 (m, 2H), 1.81−1.87 (m, 1H), 2.07−2.16 (m, 3H), 2.39−2.50 (m, 2H), 3.46 (t, J = 6.3 Hz, 2H), 3.65−3.67 (m, 1H), 3.73−3.77 (m, 1H), 4.12−4.15 (m, 1H), 4.26−4.30 (m, 1H), 4.48 (s, 2H), 5.11 (dt, J = 1.6, 10.6 Hz, 1H), 5.23 (dt, J = 1.7, 17.2 Hz, 1H), 5.81 (ddd, J = 5.0, 10.6, 17.2 Hz, 1H), 7.32 (br s, 5H); ^{13}C NMR δ u 138.6, 115.7, 80.5, 77.7, 72.8, 69.9, 37.1, 28.9, 25.6, 19.6, 18.7, 18.2, 18.1, d 139.1, 128.3, 127.6, 127.5, 82.2, 80.9, 75.5, 71.9, 25.9, 25.8, −4.1, −4.5, −4.6, −5.2; IR (cm^{-1}) 2928, 2858, 1076; MS *m*/*z* (%) 595 (M + Na, 20); HRMS calcd for $C_{33}H_{56}O_4Si_2Na$ (M + Na) 595.3615, obsd 595.3632; $[\alpha]_D$ +27 (*c* 1.31, CH_2Cl_2).

Aldehyde 14. A suspension of AD-mix-α (6.08 g) in *t*-BuOH−H_2O (1:1, v/v, 15 mL) was stirred at room temperature until both phases were clear, then cooled to 0 °C. Silyl ether **13** (870 mg, 1.52 mmol) was added dropwise over 5 min. The resulting mixture was stirred at 0 °C for 40 h. Solid $NaHSO_3$ (7.30 g) was carefully

added to the reaction mixture, which was stirred at room temperature for 1 h. The reaction mixture was then partitioned between EtOAc and brine. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give the diol as a colorless oil (718 mg, 1.19 mmol, 78% yield).

To a suspension of SiO_2 (4.0 g) in CH_2Cl_2 (13 mL) was added a solution of $NaIO_4$ (401 mg) in water (2.56 mL) at room temperature. The resulting mixture was stirred vigorously until a flaky mixture was formed. A solution of diol (504 mg, 0.83 mmol) in CH_2Cl_2 (2 mL) was added slowly and the mixture was stirred at room temperature for 12 h. The reaction mixture was then filtered and the filtrate was concentrated. The residue was chromatographed to give aldehyde **14** as a colorless oil (426 mg, 0.74 mmol, 90% yield). TLC R_f(MTBE/petroleum ether = 1:10) = 0.45; ^{1}H NMR δ 0.04 (s, 3H), 0.05 (s, 3H), 0.07 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 0.89 (s, 9H), 1.54−1.58 (m, 2H), 1.66−1.69 (m, 2H), 1.91 (ddd, J = 2.9, 6.3, 13.6 Hz, 1H), 2.12−2.19 (m, 3H), 2.41−2.47 (m, 2H), 3.46 (t, J = 6.3 Hz, 2H), 3.75−3.80 (m, 1H), 3.99 (dt, J = 6.3, 7.8 Hz, 1H), 4.14 (dd, J = 1.3, 6.2 Hz, 1H), 4.29−4.32 (m, 1H), 4.48 (s, 2H), 7.32 (br s, 5H), 9.66 (d, J = 1.4 Hz); ^{13}C NMR δ u 138.6, 80.8, 77.3, 72.9, 69.9, 37.3, 28.9, 25.6, 19.5, 18.6, 18.3, 18.0, d 202.4, 128.3, 127.6, 127.5, 82.7, 79.3, 78.1, 71.9, 25.81, 25.79, −4.5, −4.6, −4.8, −5.2; IR (cm^{-1}) 2929, 2856, 1737; MS m/z (%) 597 (M + Na, 35), 366 (10); HRMS calcd for $C_{32}H_{54}O_5Si_2Na$ (M + Na) 597.3408, obsd 597.3383; $[\alpha]_D$ +30 (c 2.51, CH_2Cl_2).

Enone 15. To a suspension of NaH (74 mg, 1.86 mmol, 60% in mineral oil) in THF (14 mL) was added a solution of dimethyl 2-oxo-heptylphosphonate (494 mg, 2.23 mmol) in THF (1 mL) at 0 °C under N_2. The resulting mixture was stirred at room temperature for 1 h. A solution of aldehyde **14** (426 mg, 0.74 mmol) in THF (1 mL) was added slowly and the mixture was stirred at room temperature for 15 min. The reaction mixture was then partitioned between ether and saturated aqueous NH_4Cl. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give enone **15** as a colorless oil (446 mg, 0.67 mmol, 90% yield). TLC R_f(MTBE/petroleum ether = 1:10) = 0.60; ^{1}H NMR δ 0.01 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H), 0.06 (s, 3H), 0.87 (s, 9H), 0.88 (s, 9H), 1.20−1.29 (m, 7H), 1.52−1.58 (m, 4H), 1.64−1.69 (m, 2H), 1.83 (ddd, J = 2.5, 6.5, 12.4 Hz, 1H), 2.05−2.15 (m, 3H), 2.39−2.49 (m, 2H), 2.53 (t, J = 7.8 Hz), 3.46 (t, J = 6.4 Hz, 2H), 3.62−3.67 (m, 1H), 3.71−3.77 (m, 1H), 4.26−4.29 (m, 1H), 4.33 (t, J = 5.7 Hz, 1H), 4.47 (s, 2H), 6.24 (d, J = 16.0 Hz, 1H), 6.76 (dd, J = 5.1, 16.0 Hz, 1H), 7.32 (br s, 5H); ^{13}C NMR δ u 200.9, 138.6, 80.7, 77.4, 72.9, 69.9, 40.3, 37.4, 31.4, 29.7, 28.9, 25.6, 23.9, 22.5, 19.6, 18.7, 18.2, 18.1, d 146.2, 129.6, 128.3, 127.6, 127.5, 82.4, 80.5, 73.9, 71.9, 25.8, 13.9, −4.2, −4.6, −5.2; IR (cm^{-1}) 2929, 1252, 1078; MS m/z (%) 693 (M + Na, 100), 539 (65); HRMS calcd for $C_{39}H_{66}O_5Si_2Na$ (M + Na) 693.4347, obsd 693.4342; $[\alpha]_D$ +48 (c 0.63, CH_2Cl_2).

Alcohol 16. To a solution of epoxide **3** (119 mg, 0.36 mmol), triphenylphosphine (501 mg, 1.81 mmol), and 4-nitrobenzoic acid (272 mg, 1.63 mmol) in THF (8 mL) was added diisopropyl azodicarboxylate (584 mg, 2.89 mmol) at 0 °C under N_2. Then the mixture was stirred at room temperature for 18 h. All the volatiles were removed and the residue was dissolved in MeOH (2 mL). Finely powdered K_2CO_3 (1.0 g) was added at 0 °C under N_2. Then the mixture was stirred at room temperature for 20 min. The reaction mixture was then partitioned between CH_2Cl_2 and water. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give alcohol **16** as a colorless oil (76 mg, 0.23 mmol, 64% yield for two steps). TLC R_f(MTBE/petroleum ether = 1:1) = 0.25; ^{1}H NMR δ1.61−1.78 (m, 5H), 1.96−2.04 (m, 2H), 2.19−2.25 (m, 3H), 2.29−2.34 (m, 1H), 2.53−2.58 (m, 1H), 2.65 (dd, J = 2.6, 4.8 Hz, 1H), 2.84 (t, J = 4.3 Hz, 1H), 3.08−3.11 (m, 1H), 3.53 (t, J = 6.3 Hz, 2H), 3.89−3.93 (m, 1H), 4.14−4.18 (m, 1H), 4.32−4.35 (m, 1H), 4.54 (s, 2H), 7.34 (br s, 5H); ^{13}C NMR δ u 138.4, 82.3, 75.9, 72.9, 69.8, 45.3, 35.8, 28.8, 25.6, 23.9, 18.5, d 128.4, 127.7, 127.6, 84.9, 78.1, 75.4, 52.9; IR (cm^{-1}) 3432, 2924, 1453; MS m/z (%) 353 (M + Na, 82), 339 (35), 279 (30); HRMS calcd for $C_{20}H_{26}O_4Na$ (M + Na) 353.1729, obsd 353.1721; $[\alpha]_D$ +3.8 (c 3.80, CH_2Cl_2).

Silyl Ether 17. To a solution of epoxide **3** (180 mg, 0.55 mmol) in CH_2Cl_2 (8 mL) was added imidazole (93 mg, 1.36 mmol) and TBDMSCl (164 mg, 1.09 mmol) at 0 °C. The resulting mixture was allowed to warm to room temperature slowly and stirred for 12 h. The reaction mixture was then partitioned between CH_2Cl_2 and water. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give silyl ether **17** as a colorless oil (222 mg, 0.50 mmol, 90% yield). TLC R_f(MTBE/petroleum ether = 1:4) = 0.35; ^{1}H NMR δ 0.09 (s, 3H), 0.10 (s, 3H), 0.89 (s, 9H), 1.53−1.58 (m, 2H), 1.65−1.70 (m, 2H), 1.96−2.00 (m, 1H), 2.11−2.17 (m, 2H), 2.22−2.30 (m, 1H), 2.44−2.49 (m, 2H), 2.65 (dd, J = 2.1, 4.2 Hz, 1H), 2.77 (dd, J = 3.0, 4.2 Hz, 1H), 3.04−3.07 (m, 1H), 3.46 (t, J = 6.3 Hz, 2H), 3.68−3.73 (m, 1H), 3.82−3.86 (m, 1H), 4.25−4.29 (m, 1H), 4.48 (s, 2H), 7.32 (br s, 5H); ^{13}C NMR δ u 138.6, 81.0, 77.0, 72.9, 69.9, 47.0, 38.7, 29.0, 25.6, 19.5, 18.6, 18.0, d 128.3, 127.6, 127.5, 83.2, 78.6, 71.9, 54.0, 25.7, −4.6, −5.2; IR (cm^{-1}) 2928, 2359, 1067; MS m/z (%) 467 (M + Na, 65); HRMS calcd for $C_{33}H_{56}O_4Si_2Na$ (M + Na) 467.2594, obsd 467.2616; $[\alpha]_D$ +34 (c 1.21, CH_2Cl_2).

Alkene 18. To a suspension of Me_3SI (345 mg, 1.69 mmol) in THF (10 mL) was added n-BuLi (2.15 M solution in hexane, 0.6 mL) at −20 to −10 °C under N_2. Then the mixture was stirred at −20 to −10 °C for 1 h. A solution of silyl ether **17** (150 mg, 0.34 mmol) in THF (1 mL) was added dropwise. The resulting mixture was allowed to warm to room temperature slowly and stirred for 10 h. The reaction mixture was then partitioned between CH_2Cl_2 and saturated aqueous NH_4Cl. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give alkene **18** as a colorless oil (104 mg, 0.23 mmol, 67% yield). TLC R_f(MTBE/petroleum ether = 1:4) = 0.50; ^{1}H NMR δ 0.09 (s, 3H), 0.11 (s, 3H), 0.91 (s, 9H), 1.55−1.58 (m, 2H), 1.62−1.70 (m, 2H), 1.90 (dd, J = 3.9, 14.0 Hz, 1H), 2.03 (ddd, J = 5.0, 9.5, 14.0 Hz, 1H), 2.13−2.18 (m, 2H), 2.47−2.50 (m, 2H), 3.19 (d, J = 2.2 Hz, 1H), 3.46 (t, J = 6.3 Hz, 2H), 3.74−3.78 (m, 1H), 4.10−4.14 (m, 1H), 4.23−4.27 (m, 1H), 4.36−4.38 (m, 1H), 4.48 (s, 2H), 5.15 (dt, J = 1.7, 10.6 Hz, 1H), 5.38 (dt, J = 1.7, 17.1 Hz, 1H), 5.71 (ddd, J = 5.0, 10.6, 17.1 Hz, 1H), 7.32 (br s, 5H); ^{13}C NMR δ u 138.5, 115.8, 81.3, 76.7, 72.9, 69.8, 33.8, 28.9, 25.6, 19.2, 18.6, 18.1, d 137.0, 128.3, 127.6, 127.5, 82.4, 80.7, 72.4, 71.8, 25.7, −4.8, −5.2; IR (cm^{-1}) 2928, 2856, 1071; MS m/z (%) 481 (M + Na, 100); HRMS calcd for $C_{27}H_{42}O_4Si_1Na$ (M + Na) 481.2750, obsd 481.2731; $[\alpha]_D$ +43 (c 1.11, CH_2Cl_2).

Alcohol 19. To a solution of alkene **18** (20 mg, 0.044 mmol), triphenylphosphine (61 mg, 0.22 mmol), and 4-nitrobenzoic acid (33 mg, 0.20 mmol) in THF (1 mL) was added diisopropyl azodicarboxylate (71 mg, 0.35 mmol) at 0 °C under N_2. Then the mixture was stirred at room temperature for 18 h. All the volatiles were removed and the residue was chromatographed to give benzoyl ester as a white solid (12 mg, 0.020 mmol, 45% yield). TLC R_f(MTBE/petroleum ether = 1:4) = 0.55; mp 65−67 °C; ^{1}H NMR δ 0.07 (s, 3H), 0.09 (s, 3H), 0.93 (s, 9H), 1.50−1.55 (m, 2H), 1.61−1.68 (m, 2H), 1.84 (ddd, J = 1.8, 4.1, 13.7 Hz, 1H), 2.08−2.13 (m, 2H), 2.21 (ddd, J = 5.3, 8.8, 13.7 Hz, 1H), 2.40−2.47 (m, 2H), 3.43 (t, J = 6.4 Hz, 2H), 3.85−3.90 (m, 1H), 4.14−4.20 (m, 1H), 4.30−4.32 (m, 1H), 4.47 (s, 2H), 5.32 (d, J = 10.5 Hz, 1H), 5.43 (d, J = 16.2 Hz, 1H), 5.69 (dd, J = 7.3, 7.8 Hz), 5.84 (ddd, J = 7.3, 10.5, 16.2 Hz, 1H), 7.32 (br s, 5H), 8.24 (br s, 4H); ^{13}C NMR δ u 163.8, 150.4, 138.5, 136.0, 120.2, 80.8, 77.1, 72.8, 69.8, 37.2, 28.9, 25.6, 19.7, 18.6, 18.1, d 132.8, 130.8, 128.3, 127.6, 127.5, 123.4, 83.1, 78.6, 78.4, 71.7, 25.8, −4.5, −5.3; MS m/z (%) 630 (M + Na, 25); HRMS calcd for $C_{34}H_{45}O_7SiNNa$ (M + Na) 630.2863, obsd 630.2893; $[\alpha]_D$ +26 (c 1.81, CH_2Cl_2).

To a solution of benzoyl ester (12 mg, 0.020 mmol) in MeOH (0.5 mL) was added finely powdered K_2CO_3 (250 mg, 1.81 mmol) at 0 °C under N_2. Then the mixture was stirred at room temperature

for 30 min. The reaction mixture was then partitioned between CH_2Cl_2 and water. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give alcohol **19** as a colorless oil (8 mg, 0.018 mmol, 90% yield). TLC R_f(MTBE/petroleum ether = 1:4) = 0.30; ^{1}H NMR δ 0.08 (s, 3H), 0.10 (s, 3H), 0.90 (s, 9H), 1.54−1.59 (m, 2H), 1.65−1.70 (m, 2H), 1.82 (ddd, J = 1.1, 4.0, 13.7 Hz, 1H), 2.12−2.16 (m, 2H), 2.20 (ddd, J = 5.2, 9.2, 13.7 Hz, 1H), 2.45−2.48 (m, 2H), 2.98 (d, 3.8 Hz, 1H), 3.46 (t, J = 6.4 Hz, 2H), 3.81 (ddd, J = 3.2, 7.4, 6.6 Hz, 1H), 3.95 (ddd, J = 4.0, 5.4, 9.3 Hz, 1H), 4.02−4.07 (m, 1H), 4.26−4.29 (m, 1H), 4.48 (s, 2H), 5.17 (d, J = 10.3 Hz, 1H), 5.32 (d, J = 17.1 Hz, 1H), 5.83 (ddd, J = 6.5, 10.3, 17.1 Hz, 1H), 7.32 (br s, 5H), 8.24 (br s, 4H); ^{13}C NMR δ u 138.5 116.8, 81.2, 76.9, 72.9, 69.9, 37.4, 28.9, 25.6, 19.4, 18.6, 18.1, d 137.5, 128.3, 127.6, 127.5, 82.7, 80.9, 75.4, 72.0, 25.8, −4.7, −5.2; MS m/z (%) 481-(M + Na, 25); HRMS calcd for $C_{27}H_{42}O_4SiNa$ (M + Na) 481.2750, obsd 481.2732; $[\alpha]_D$ +39 (c 0.75, CH_2Cl_2).

Alcohol 20. To a solution of (−)-DIP-Cl (483 mg, 1.50 mmol) in THF (15 mL) was added a solution of enone **15** (500 mg, 0.75 mmol) in THF (2 mL) at −78 °C under N_2. The resulting mixture was allowed to warm to room temperature slowly and stirred for 24 h. Then the reaction mixture was partitioned between CH_2Cl_2 and sequentially 1 N aqueous NaOH and saturated aqueous NH_4-Cl. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give alcohol **20** as a colorless oil (428 mg, 0.64 mmol, 85% yield). TLC R_f-(MTBE/petroleum ether = 1:4) = 0.25; ^{1}H NMR δ 0.02 (s, 3H), 0.04 (s, 3H), 0.05 (s, 6H), 0.87 (s, 9H), 0.88 (s, 9H), 1.20−1.29 (m, 7H), 1.45−1.58 (m, 5H), 1.65−1.70 (m, 3H), 1.84 (ddd, J = 3.5, 7.1, 13.3 Hz, 1H), 2.07−2.16 (m, 3H), 2.36−2.43 (m, 2H), 3.46 (t, J = 6.4 Hz, 2H), 3.61 (dd, J = 7.1, 16.2 Hz, 1H), 3.72−3.78 (m, 1H), 4.05−4.11 (m, 1H), 4.13−4.20 (m, 1H), 4.26−4.33 (m, 1H), 4.48 (s, 2H), 5.65 (t, J = 4.8 Hz, 2H), 7.32 (br s, 5H); ^{13}C NMR δ u 138.6, 80.6, 77.7, 72.8, 69.9, 37.3, 37.1, 31.7, 28.9, 25.6, 25.0, 22.6, 19.7, 18.7, 18.2, 18.1, d 134.3, 131.4, 128.3, 127.6, 127.5, 82.1, 81.1, 74.5, 72.3, 72.0, 25.9, 25.8, 14.0, −3.9, −4.5, −5.2; IR (cm^{-1}) 3429, 2928, 1250; MS m/z (%) 695 (M + Na, 85), 523 (75); HRMS calcd for $C_{39}H_{68}O_5Si_2Na$ (M + Na) 695.4503, obsd 695.4520; $[\alpha]_D$ +21 (c 1.01, CH_2Cl_2).

Silyl Ether 22. To a solution of alcohol **20** (584 mg, 0.87 mmol) in CH_2Cl_2 (11 mL) was added imidazole (148 mg, 2.17 mmol) and TBDMSCl (262 mg, 1.74 mmol) at 0 °C. The resulting mixture was allowed to warm to room temperature slowly and stirred for 12 h. The reaction mixture was then partitioned between CH_2Cl_2 and water. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give silyl ether **22** as a colorless oil (622 mg, 0.79 mmol, 91% yield). TLC R_f-(MTBE/petroleum ether = 1:10) = 0.75; ^{1}H NMR δ 0.00 (s, 3H), 0.02 (s, 6H), 0.04 (s, 3H), 0.05 (s, 3H), 0.06 (s, 3H), 0.86 (s, 9H), 0.87 (s, 9H), 0.88 (s, 9H), 1.17−1.28 (m, 7H), 1.29−1.44 (m, 2H), 1.45−1.58 (m, 3H), 1.65−1.70 (m, 3H), 1.81−1.88 (m, 1H), 2.00−2.05 (m, 1H), 2.12−2.16 (m, 2H), 2.36−2.44 (m, 2H), 3.46 (t, J = 6.4 Hz, 2H), 3.57−3.63 (m, 1H), 3.71−3.76 (m, 1H), 4.06 (dd, J = 6.4, 12.6 Hz, 1H), 4.23 (t, J = 5.2 Hz, 1H), 4.27−4.31 (m, 1H), 4.48 (s, 2H), 5.47 (dd, J = 5.5, 15.4 Hz, 1H), 5.61 (dd, J = 6.4, 15.4 Hz, 1H), 7.32 (br s, 5H); ^{13}C NMR δ u 138.6, 80.3, 77.9, 72.8, 69.9, 38.3, 36.4, 31.8, 28.9, 25.7, 24.9, 22.6, 19.7, 18.7, 18.26, 18.24, 18.1, d 134.7, 130.0, 128.3, 127.6, 127.5, 82.0, 81.0, 73.6, 73.1, 72.1, 25.9, 25.8, 14.0, −4.2, −4.3, −4.6, −4.8, −5.2; IR (cm^{-1}) 2928, 1471, 1253; MS m/z (%) 809 (M + Na, 98), 655 (100); HRMS calcd for $C_{45}H_{82}O_5Si_3Na$ (M + Na) 809.5368, obsd 809.5401; $[\alpha]_D$ +19 (c 0.25, CH_2Cl_2).

Alkene 24. To a solution of $Ni(OAc)_2 \cdot 4H_2O$ (152 mg, 0.61 mmol) in ethanol (6 mL) was add a solution of $NaBH_4$ (1N in ethanol, 0.61 mL, 0.61 mmol). The black mixture was evacuated and backfilled with H_2 three times. Ethylenediamine (0.05 mL, 0.67 mmol) was added, followed by a solution of silyl ether **22** (480 mg, 0.61 mmol) in ethanol (1 mL). The flask was evacuated and backfilled with H_2 three times. The reaction mixture was stirred at room temperature for 10 h under H_2. The black suspension was filtered through a short column packed with flash silica gel. The column was eluted with MTBE (100 mL). The solvent was removed to give the alkene **24** as a colorless oil (427 mg, 0.54 mmol, 89% yield). TLC R_f(MTBE/petroleum ether = 1:10) = 0.85; ^{1}H NMR δ 0.00 (s, 3H), 0.02 (s, 6H), 0.03 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H), 0.86 (s, 9H), 0.87 (s, 9H), 0.88 (s, 9H), 1.19−1.30 (m, 9H), 1.36−1.47 (m, 4H), 1.58−1.65 (m, 2H), 1.81−1.87 (m, 1H), 2.02−2.08 (m, 3H), 2.23−2.33 (m, 2H), 3.45 (t, J = 6.3 Hz, 2H), 3.50−3.58 (m, 2H), 4.05 (dd, J = 6.2, 12.4 Hz, 1H), 4.22−4.31 (m, 2H), 4.48 (s, 2H), 5.41−5.51 (m, 3H), 5.61 (dd, J = 6.5, 15.4 Hz, 1H), 7.31 (br s, 5H); ^{13}C NMR δ u 138.7, 72.8, 70.4, 38.4, 36.8, 31.8, 29.4, 27.7, 27.2, 26.2, 24.9, 22.6, 18.3, 18.2, 18.1, d 134.5, 130.7, 130.2, 128.3, 127.6, 127.4, 126.9, 83.2, 80.9, 73.6, 73.2, 72.8, 25.9, 25.8, 14.0, −4.2, −4.3, −4.5, −4.8, −5.1; IR (cm^{-1}) 2928, 1471, 1253; MS m/z (%) 811 (M + Na, 100), 657 (95); HRMS calcd for $C_{45}H_{84}O_5Si_3Na$ (M + Na) 811.5524, obsd 811.5543; $[\alpha]_D$ +4 (c 1.62, CH_2Cl_2).

Alcohol 26. To a solution of naphthalene (146 mg, 1.14 mmol) in THF (2 mL) was added lithium metal (5.3 mg, 0.76 mmol) at room temperature under N_2. The mixture was stirred at room temperature until a dark green solution was formed. Then it was cooled to −25 °C and a solution of alkene **24** (30 mg, 0.04 mmol) in THF (0.5 mL) was added. The mixture was stirred at −25 °C for 1 h. The reaction mixture was then partitioned between ether and saturated aqueous NH_4Cl. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give alcohol **26** as a colorless oil (25 mg, 0.037 mmol, 94% yield). TLC R_f(MTBE/petroleum ether = 1:4) = 0.45; ^{1}H NMR δ 0.00 (s, 3H), 0.02 (s, 6H), 0.03 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H), 0.86 (s, 9H), 0.87 (s, 9H), 0.88 (s, 9H), 1.19−1.27 (m, 8H), 1.33−1.44 (m, 4H), 1.53−1.58 (m, 3H), 1.84−1.87 (m, 1H), 2.02−2.08 (m, 3H), 2.26−2.33 (m, 2H), 3.52−3.57 (m, 2H), 3.62 (t, J = 6.5 Hz, 2H), 4.04 (dd, J = 6.2, 12.4 Hz, 1H), 4.19−4.25 (m, 2H), 5.37−5.53 (m, 3H), 5.61 (ddd, J = 1.2, 6.5, 15.4 Hz, 1H); ^{13}C NMR δ u 62.9, 38.4, 36.8, 32.4, 31.8, 27.7, 27.1, 25.7, 24.9, 22.6, 18.3, 18.2, 18.1, d 134.6, 130.5, 130.1, 127.1, 83.1, 80.9, 73.6, 73.2, 72.8, 25.9, 25.8, 14.0, −4.2, −4.3, −4.5, −4.6, −4.8, −5.1; IR (cm^{-1}) 3339, 2954, 1472; MS m/z (%) 721 (M + Na, 35); HRMS calcd for $C_{38}H_{78}O_5Si_3Na$ (M + Na) 721.5055, obsd 721.5073; $[\alpha]_D$ +9 (c 1.25, CH_2Cl_2).

Acid 28. To a solution of alcohol **26** (25 mg, 0.036 mmol) in DMF (0.5 mL) was added water (1 drop), followed by PDC (88 mg, 0.233 mmol). The mixture was stirred at room temperature for 15 h. The dark brown suspension was filtered through a short column packed with flash silica gel. The column was eluted with MTBE (50 mL) and then concentrated. The residue was chromatographed to give acid **28** as a colorless oil (13 mg, 0.018 mmol, 51% yield). TLC R_f(ether/5% aqueous NaH_2PO_4 = 10:1, ether layer) = 0.50; ^{1}H NMR δ 0.00 (s, 3H), 0.02 (s, 6H), 0.03 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H), 0.85 (s, 9H), 0.86 (s, 9H), 0.88 (s, 9H), 1.17−1.32 (m, 8H), 1.34−1.48 (m, 3H), 1.65−1.72 (m, 2H), 1.80−1.87 (m, 1H), 2.02−2.11 (m, 3H), 2.22−2.28 (m, 2H), 3.31−3.38 (m, 2H), 3.53−3.58 (m, 2H), 4.06 (dd, J = 6.1, 12.3 Hz, 1H), 4.22−4.26 (m, 2H), 5.36−5.53 (m, 3H), 5.61 (ddd, J = 0.8, 6.5, 15.5 Hz, 1H); ^{13}C NMR δ u 178.3, 38.4, 36.8, 33.2, 31.8, 27.7, 26.6, 24.9, 24.5, 22.6, 18.3, 18.1, d 134.6, 130.1, 129.4, 128.1, 83.1, 80.9, 73.6, 73.2, 72.8, 25.89, 25.84, 14.1, −4.2, −4.3, −4.5, −4.6, −4.8, −5.1; IR (cm^{-1}) 2928, 1710, 1472; MS m/z (%) 735 (M + Na, 70), 394 (100); HRMS calcd for $C_{38}H_{76}O_6Si_3Na$ (M + Na) 735.4847, obsd 735.4855; $[\alpha]_D$ +2.8 (c 2.06, CH_2Cl_2).

Acid 29. To a solution of alcohol **27** (118 mg, 0.169 mmol) in CH_2Cl_2 (2.0 mL) was added a solution of Dess−Martin periodate (80 mg, 0.187 mmol) in CH_2Cl_2 (2 mL) under N_2. After 30 min, the reaction mixture was diluted with ether (20 mL) and NaOH (1.0 M, 1.5 mL) was added. The reaction mixture was stirred at room temperature for an additional 10 min and then partitioned between ether and water. The combined organic extracts were dried

(Na_2SO_4) and concentrated. The residue was used directly for the next reaction.

To a solution of NaH_2PO_4 (28 mg) in water (0.5 mL) was added $NaClO_2$ (37 mg) at room temperature. Then a solution of crude aldehyde in MTBE (1.0 mL) was added. The mixture was stirred vigorously at room temperature overnight and then partitioned between ether and water. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give acid **29** as a colorless oil (106 mg, 0.185 mmol, 88% yield for two steps). TLC R_f(ether/5% aqueous NaH_2PO_4 = 10:1, ether layer) = 0.50; ^{1}H NMR δ 0.00 (s, 3H), 0.01 (s, 3H), 0.02 (s, 6H), 0.03 (s, 3H), 0.05 (s, 3H), 0.86 (s, 9H), 0.87 (s, 9H), 0.88 (s, 9H), 1.17−1.32 (m, 8H), 1.34−1.48 (m, 3H), 1.65−1.72 (m, 2H), 1.80−1.87 (m, 1H), 2.02−2.12 (m, 3H), 2.22−2.28 (m, 2H), 3.31−3.35 (m, 2H), 3.53−3.59 (m, 2H), 4.07 (dd, J = 4.8, 9.9 Hz, 1H), 4.22−4.26 (m, 2H), 5.36−5.53 (m, 3H), 5.61 (dd, J = 4.8, 12.9 Hz, 1H); ^{13}C NMR δ u 178.8, 38.3, 36.8, 33.3, 31.8, 27.7, 26.6, 24.9, 24.5, 22.7, 18.3, 18.1, d 134.6, 129.9, 129.4, 128.0, 83.1, 80.9, 73.8, 73.0, 72.7, 25.89, 25.84, 14.1, −4.2, −4.3, −4.5, −4.6, −4.9, −5.1; IR (cm^{-1}) 2929, 2857, 1710; MS *m*/*z* (%) 735 (M + Na, 70), 394 (100); HRMS calcd for $C_{38}H_{76}O_6Si_3Na$ (M + Na) 735.4847, obsd 735.4873; $[\alpha]_D$ +14 (*c* 0.375, CH_2Cl_2).

IsoF 2a. To a solution of acid **28** (64 mg, 0.090 mmol) in THF (0.5 mL) was added TBAF (3 M solution in THF, 0.9 mL). The mixture was stirred at room temperature for 24 h and concentrated. The residue was chromatographed to give isoF **2a** as a colorless oil (22 mg, 0.058 mmol, 65% yield). TLC R_f(ether/5% aqueous NaH_2PO_4/HOAC = 100:10:1, ether layer) = 0.45; ^{1}H NMR δ 0.85 (t, J = 4.9 Hz, 3H), 1.17−1.33 (m, 6H), 1.41−1.50 (m, 2H), 1.64−1.72 (m, 2H), 1.93 (d, J = 14.1 Hz, 1H), 2.09−2.18 (m, 3H), 2.29−2.40 (m, 3H), 2.46−2.51 (m, 1H), 3.66 (t, J = 5.7 Hz, 1H), 4.02−4.09 (m, 3H), 4.36 (d, J = 5.4 Hz, 1H), 5.41−5.47 (m, 2H), 5.50 (dd, J = 5.9, 15.7 Hz, 1H), 5.76 (dd, J = 5.9, 15.7 Hz, 1H); ^{13}C NMR δ u 177.9, 36.9, 34.0, 33.1, 31.7, 27.2, 26.4, 25.1, 24.4, 22.6, d 135.7, 130.7, 128.8, 126.8, 83.5, 80.2, 72.3, 72.0, 70.9, 14.0; IR (cm^{-1}) 3438, 2928, 1710; MS *m*/*z* (%) 393 (M + Na, 66), 335 (100); HRMS calcd for $C_{20}H_{34}O_6Na$ (M + Na) 393.2253, obsd 393.2241; $[\alpha]_D$ +14 (*c* 0.485, CH_2Cl_2).

IsoF 2b. The same procedure was applied as for the preparation of **2a**. IsoF **2b** was prepared as a colorless oil (23 mg, 0.061 mmol, 68% yield). TLC R_f(ether/5% aqueous NaH_2PO_4/HOAC = 100:10:1, ether layer) = 0.45; ^{1}H NMR δ 0.86 (t, J = 6.9 Hz, 3H), 1.17−1.33 (m, 6H), 1.41−1.50 (m, 2H), 1.66−1.73 (m, 2H), 1.91 (dd, J = 2.7, 14.2 Hz, 1H), 2.07−2.19 (m, 3H), 2.29−2.37 (m, 3H), 2.48−2.53 (m, 1H), 3.67−3.70 (m, 1H), 4.00−4.02 (m, 1H), 4.07−4.11 (m, 2H), 4.40−4.42 (m, 1H), 5.45−5.48 (m, 2H), 5.55 (dd, J = 4.7, 15.6 Hz, 1H), 5.81 (dd, J = 4.7, 15.6 Hz, 1H); ^{13}C NMR δ u 177.8, 37.1, 33.9, 33.1, 31.7, 27.2, 26.4, 25.1, 24.4, 22.6, d 135.4, 131.1, 129.4, 127.3, 84.1, 80.3, 72.8, 72.1, 71.4, 14.5; IR (cm^{-1}) 3442, 2930, 1706; MS *m*/*z* (%) 393 (M + Na, 66), 335 (100); HRMS calcd for $C_{20}H_{34}O_6Na$ (M + Na) 393.2253, obsd 393.2237; $[\alpha]_D$ −5.5 (*c* 0.365, CH_2Cl_2).

Acknowledgment. We thank the National Institutes of Health (GM42056) for support of this work.

Note Added after ASAP Publication. There was an error in Scheme 2 in the version posted ASAP Dec. 31, 2005; the corrected version posted Jan. 4, 2006.

Supporting Information Available: General experimental procedures, experimental procedures for the **2b** series, and spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO051889A